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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,308	02/16/2001	Annelise E. Barron	6374	7049

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/788,308	BARRON ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *28-31* is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Amendment and Response filed April 12, 2004 has been entered and considered. Non-elected Claims 18-27 have been cancelled. Therefore, Claims 1-17 and 28-31 are pending and have been considered on the merits in this Office Action.

Sequences in Compliance

The objections to the Specification and Claims for being out of compliance with the sequence rules has been withdrawn in light of the amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-6, 8, 14-15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended Claims 3, 6, 14, and 17 do not follow consistently from Claim 1 (dep. Clms 3 and 6) and Claim 9 (clms 14 and 17). Claims 1 and 9 encompass a spreading agent comprising almost any amino acid sequence as long as it contains an N-substituted glycine and at least one amino acid found in a SP-B or SP-C sequence. Claims 3, 6, 14, and 17 add the limitation that at least one of residues 1-25 of SP-B

(clms 3 and 14) or 1-35 of SP-C (clms 6 and 17) is replaced with an N-substituted glycine residue. Thus, the metes and bounds of claims 3, 6, 14, and 17 are unclear. Does the limitation of the claims mean that the "at least one amino acid residue corresponding to SP-B or SP-C" of Claim 1 or 9 is substituted with an N-substituted glycine or that the spreading agent comprises a peptide having the sequence of residues 1-25 of SP-B (clms 3 and 14) or 1-35 of SP-C (clms 6 and 17) wherein at least one of the recited residues is replaced with an N-substituted glycine?
Claims 4-5, 8, and 15 are rejected because they depend from the claims above but do not correct the deficiencies. Clarification is required.

The rejection of Claims 7 and 16 under 35 U.S.C. 12, second paragraph has been **withdrawn**. These claims have been interpreted to encompass a non-natural heteropolymeric pulmonary spreading agent that contains an N-substituted glycine and at least one amino acid that is contained within the sequence of residues 5-32 of SP-C.

The rejection of Claims 3 and 15 under 35 U.S.C. 112, second paragraph is **withdrawn** in light of the amendments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-natural heteropolymeric pulmonary

spreading agent comprising a modified surfactant associated protein-C (SP-C) comprising at least one N-substituted glycine residue and wherein the modified SP-C maintains a membrane-spanning alpha helix and the activity of reducing alveolar surface tension or the non-natural heteropolymeric pulmonary spreading agents disclosed in the present Specification, does not reasonably provide enablement for a non-natural heteropolymeric pulmonary spreading agent comprising at least one N-substituted glycine residue and any amino acid sequence or a modified surfactant protein B (SP-B) containing at least one N-substituted glycine residue . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The reasons for rejection given in the previous Office Action have been repeated following the response to Applicants arguments.

Response to Applicants arguments

Applicants argue that incorporation of N-substituted glycine monomers to achieve SP-B mimics is not complex given the disclosure for SP-C and that SP-B_{1-25} has the same activity and known amphipathic structure as SP-B thus dictating that the mimic should have helical structure. This argument has been considered but is not deemed persuasive. First, the claims are drawn to a spreading agent that has any amino acid sequence and not just substitution of a N-substituted glycine into the SP-B sequence. Second, Applicants have not addressed the evidence provided by the examiner that those of skill in the art considered that SP-B is a much more complex molecule than SP-

C. As stated in the previous Office Action, Nilsson et al. describe the properties of a peptide (KL2.3; a 21 amino acid peptide) with an amphipathic helix that resembles the helices of SP-B but that does not accelerate lipid spreading effectively (p. 120, section spanning column) like SP-B. Nilsson et al. conclude that SP-B is a much more complex molecule than SP-C. This evidence suggests that one of skill in the art would consider that results from SP-C cannot necessarily be applied to SP-B mimics.

Applicants argue that peptides of any sequence up to 50-60 monomers in length can easily be synthesized and tested for helical structure and activity. This argument has been considered but is not deemed persuasive. To teach that random peptides can be made and tested is not adequate guidance as to the nature of the polypeptoid molecules that may be constructed, but is merely an invitation to the artisan to use the disclosed SP-B and SP-C peptides as a starting point for further experimentation.

The Declaration of Annelise E. Barron filed April 12, 2004 and Applicants response regarding the Declaration have been considered. The Declaration shows the synthesis and testing of 3 polypeptoids that are not similar to SP-B in sequence but have similar structural features to SP-B. All mimics tested were 17 monomers in length and all have the general structure wherein lysine side chains (hydrophilic) occur every third monomer separated by hydrophobic side chain. The Declaration states that SP-B mimics were designed to capture 3 main features of the N-terminal segment of SP-B thought to be important to its function: 1) helicity, 2) hydrophobicity, and 3) cationic and non-polar faces and that the mimics contained at least one half alpha chiral side chains, an alpha

chiral, aromatic face, and a C-terminal alpha chiral, aromatic side chain. These features were not taught in the present Specification. Moreover, contrary to Applicants suggestion of great diversity in the peptides that can be used, the Declaration and Specification provide evidence of a required structure. However, the claims are drawn to peptides of any structure. Thus, the Declaration does not overcome the rejection because 1) the guidance provided therein does not appear to be present in the present Specification, and 2) the claims are drawn to peptides of any sequence and structure whereas the Declaration appears to indicate that a specific structure is required for activity. With regard to 1), the issue is not whether or not SP-B mimics can be successfully made but rather that the Specification did not teach how to make SP-B mimics that would be successful as a spreading agent. The Specification did not provide any guidance or examples of what structural features of the SP-B structure were required for activity. The SP-B mimics and guidance on how to design them as described in the Declaration were not provided in the Application as filed.

The examiner also points out that while the specific SP-C mimics provided in the Specification have different sequences (see Fig. 7a-7c), they also have a common core structure: (hydrophobic residue)$_4$ (hydrophilic residue) (hydrophobic residue) (hydrophilic residue)$_2$ (hydrophobic residue) $_{6 \text{ or } 14}$. It appears that describing the claimed spreading agents by their structural similarity to SP-B and SP-C might be more appropriate than by the sequence of SP-B and SP-C.

Rejection:

Undue experimentation would be required to make the full scope of spreading agents that could be successfully used for their desired purpose (a spreading agent). Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims:

The claims only require that the spreading agent contain at least one N-substituted glycine and at least one residue corresponding to either SP-B or SP-C. The phrase "at least one residue corresponding to" is interpreted as encompassing any protein with an amino acid in common with an amino acid found in SP-B or SP-C and thus encompasses any amino acid sequence that has at least one N-substituted glycine.

Nature of the Invention:

The invention involves the design polypeptoid spreading agents based on SP-B and SP-C sequences that will offer protease resistance and thus will have lower immunogenicity as compared to the natural surfactant associated proteins. With respect to spreading agents based on the SP-C sequence, evidence suggests that the

SP-C sequence is less important than the maintenance of a membrane-spanning alpha helix for promoting rapid spreading of lipid mixtures (see Nilsson et al. discussed below). On the other hand, evidence suggests that a simple amphipathic helical peptide does not mimic the surface properties of SP-B (see Nilsson et al. discussed below). Furthermore, SP-B is significantly larger than SP-C and has a tertiary fold of several amphipathic helices in a dimeric structure. Thus, it appears that a membrane spanning alpha helix is required to maintain the activity of SP-C and that making a synthetic spreading agent with N-substituted glycines based on SP-B sequence is highly complex.

Amount of direction or guidance presented and Presence or Absence of Working Examples:

The present Specification refers to several references to show that making polypeptoids is well known in the prior art. The Specification provides several examples of the production of a variety of polypeptoid spreading agents based on the sequence of SP-C. The examples show that the SP-C based polypeptoids improve surface activity, improve respreading of DPPC, and that addition of SP-C mimics to lung surfactant does not adversely effect static and dynamic behavior of the lung surfactant. Example 8 provides evidence that the SP-C mimics maintain a helical secondary structure like that of natural SP-C.

There are no examples of SP-B based polypeptoids and the Specification does not provide any guidance as to how such molecules could be made that would maintain the activity of reducing alveolar surface tension possessed by the natural SP-B.

State of the prior art and Relative skill of those in the prior art:

The prior art provides evidence that the SP-C primary structure (sequence) is not as important as its secondary structure (maintaining its transmembrane alpha helical structure) and that one of ordinary skill in the art was able to make mutations in the protein and maintain the alpha helical structure (see Nilsson et al. Eur. J. Biochem. (1998) 255: 116-124; specifically p. 123, Col. 2, 1st paragraph). Nilsson et al. show that an optimally alpha helical SP-C based substitute (WMAP10; see p. 121, Col. 1, 2nd paragraph and Fig. 1) and an SP-C based substitute wherein all helical valine residues are replaced with Leucines and the palmitoylcysteines at positions 5 and 6 are replaced with serine maintains its helical structure and spreading properties of native SP-C. Thus Nilsson et al. appears to provide evidence that the SP-C sequence may be modified considerably without loss of activity as long as its transmembrane alpha helical nature is not disturbed and that those of skill in the art were able to optimize the helical nature of SP-C.

Nilsson et al. also describe the properties of a peptide with an amphipathic helix that resembles the helices of SP-B but that does not accelerate lipid spreading effectively (p. 120, section spanning columns) like SP-B. Nilsson et al. conclude that SP-B is a much more complex molecule than SP-C.

Predictability:

For the reasons stated above, designing a peptoid having any sequence or a peptoid based on the SP-B sequence that would maintain the property of reducing alveolar surface tension possessed by natural SP-B and SP-C is highly unpredictable.

Quantity of Experimentation:

Because the claims only require one amino acid in common with SP-B and SP-C, a large quantity of experimentation would be necessary to generate the infinite number of polypeptoid molecules recited in the claims and possibly screen same for activity.

To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the characterization of the properties of SP-B which are required to maintain its activity and the discovery of active SP-C mimics that do not have alpha helical structure. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a spreading agent which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Conclusions

Claims 28-31 appear to be in condition for allowance. Claims 1-17 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Holly Schnizer
June 16, 2004